B2 cont C1 cont'd interaction between AGE and cellular RAGE].

REMARKS

Claims 1-35 are pending. Claims 11 and 28 have been canceled without prejudice. Claims 1 and 19 have been amended to more particularly point out the presently claimed invention. Support for these amendments may be found inter alia in the specification. Support for the amendments to claim 1 and 19 may be found in the subject specification on page 6, lines 18-25. Furthermore, support for "inhibit progression of" may be found on page 34, lines 26-30. Support for "prevent accelerated development of atherosclerosis" may be found on page 32, lines 3-7. Applicants maintain that these amendments raise no issue of new matter. Thus, claims 1-10, 12-27 and 29-35 are pending.

Withdrawal of Rejections

Applicants note and appreciate that the Examiner withdrew the rejections of claims 1-35 as being unpatentable over Neeper et al., J. Biol. Chem. 267(1): 14998-15004, July 25, 1992, in view of Schmidt et al., Artheriosclerosis and Thrombosis 14(10): 1521-1528, cited by applicants, and Bernton, U.S. Patent 5,605,885(A).

The Examiner also withdrew the rejections of claims 1-35 as being anticipated or obvious over Wautier et al., J. Clim. Invest. 97(1): 238-243, January 1996.

Sequence Listing

The Examiner stated that this application fails to comply with the requirements of 37 C.F.R. §1.821 through §1.825 for the reason set forth on the Notice to Comply With Requirements For Patent Applicatins Containing Nucleotide Sequence And/Or Amino

Acid Sequence Disclosures. A copy of the Notice is attached hereto as **Exhibit A**.

In reply to the Notice, applicants submit herewith a Sequence Listing in computer readable form (CRF) (ASCII DOS format) on the enclosed computer diskette. Applicants submit a paper copy of the Sequence Listing herewith as **Exhibit B** and maintain that the information on the CRF is identical to that contained in the paper copy. Lastly, applicants submit as **Exhibit C**, a Statement In Accordance With 37 C.F.R. §1.821(f) certifying that the CRF submitted herewith has the same information as the paper copy which is attached hereto as **Exhibit B**. Thus, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection.

Rejections Under 35 U.S.C. §112, first paragraph

The Examiner maintained the rejection of claims 1-35 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for "a polypeptide derived from soluble receptor for advanced glycation end product". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner further stated applicant has amended claims 1 and 19 by incorporating the amino acid sequences of bovine (SEQ ID No: 2) and human (SEQ ID No: 4) RAGE disclosed by Neeper et al., J.Biol.Chem. 267(1):14998-15004, July 25, 1992. However, the Examiner stated that the claims remain rejected because the claims are to a polypeptide derived from soluble receptor, and that the term "derivative" encompasses chemical modification, mutated forms, conjugates, etc..., and that it is unpredictable which molecule would be functional.

The Examiner noted the applicants arguments that the specification fully enables "a polypeptide derived from soluble receptor for advanced glycation product" have been considered but have not been found persuasive. The Examiner stated that applicants' reference to examples on page 12, line 21 to page 13, line 1, and page 10 starting line 11, were not persuasive to the Examiner and according to the Examiner do not address the rejection, because either no example is disclosed in the cited sections, or there is no clear structural definition provided. There is not working example commensurate in scope with the unlimited number of structures possible. Provision of a full description of conservative substitutions of sRAGE is not persuasive to the Examiner because, even though it is routine in the current state of the art to make mutants, no guidance is provided about which mutant, if any, has an activity, and it would require undue experimentation for one of skill in the art to make the invention according to the Examiner.

The Examiner further noted applicants include in their definition of the polypeptide of the present invention, a peptidomimetic compound (page 11, line 1) which may be at least partially unnatural. The Examiner stated that considering the multitude of possible structures and not knowing what the active part of the molecule is one of skill in the art would not know how to make and/or use the invention.

In addition, the Examiner maintained the rejection of claims 1-35 under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement "to prevent accelerated atherosclerosis in a subject predisposed thereto", or "to prevent a macrovessel disease in a subject predisposed thereto". The Examiner stated that the specification discloses an example (page 32, line 33, page 34, line 25+) of treatment of artificially induced diabetic mice with sRAGE, and an example of prevention in artificially induced diabetic mice (Figure 3), but the

specification is not enabled for a method of prevention of accelerated atherosclerosis or a macrovessel disease. The Examiner stated that the example provided refers to a case of artificially induced diabetes, where the time of start of the disease is clearly known, where the evolution of the disease is monitored, and where intervention is practiced at an early stage, like possibly a stage where the AGEs are not "sticking" to the cell walls and wherein a soluble form of RAGE can possible "trap" the AGEs. It is the Examiner's position that athriosclerosis and macrovessel diseases are usually diseases that develop over an extended period of time, that do not show symptoms for long periods of time, and for which the "starting point" is unknown. Furthermore, the Examiner asserted that even if numerous risk factors for athriosclerosis have been cited in the medical and scientific literature, there is no clear parameter defining who is predisposed to develop it, at which stage of their life, under which circumstances, and how and when the polypeptide should be administered. The Examiner further asserted that the susceptibility to atherosclerosis an macrovessel disease varies greatly among individuals exposed to identical risk factors, and it is allegedly unpredictable which individual is going to develop the disease and over which period of time. The Examiner took the position that the specification does not provide guidance about how to determine who is predisposed to develop the diseases or at which stage of the disease the polypeptide should be administered. The Examiner stated that it is unpredictable if the preventing will work in an established or an advanced stage of disease, in a case of naturally occurring diabetes in human for example. The Examiner stated that it is allegedly even less predictable if the preventing method would work in other diseases where atheriosclerosis and macrovessel disease are not associated specifically with diabetes, like different types of hyperlipidemia or hypothyroidism.

While the Examiner agrees that numerous risk factors are known

(like high blood pressure, obesity) and may play a role in the development of vascular diseases, the Examiner stated that it is still unpredictable to determine who is predisposed to develop the vascular diseases (like for example which person drinking soft as opposed to hard water), and who would be prevented from developing the disease through the administration of a polypeptide derived form soluble receptor for advanced glycation product. Further, the Examiner stated that the model system used (artificially induced diabetes in mice) is not predictive of prevention in such patients, for reasons cited above.

In reply, applicants respectfully traverse the rejection under 35 U.S.C. §112, first paragraph. The claimed invention is fully enabled by the subject specification.

As to the Examiner's concern regarding "a polypeptide derived from soluble receptor for advanced glycation end product," applicants direct the Examiner's attention to the amendments presented hereinabove to claims 1 and 19. Applicants do not concede the correctness of the Examiner's statements, but have amended claims 1 and 19 to characterize the polypeptide as comprising the V-domain of sRAGE or a derivative thereof capable of inhibiting the interaction between AGE and RAGE. Applicants submit that the presently claimed invention is fully enabled. The V-domain of sRAGE is described in the specification on page 6 and has been identified in Figures 3 and 5 from Neeper et al. See also page 6, line 18-24 of the subject specification. The sequence of bovine and human RAGE is provided in the subject specification as Figures 4A-4B (Seq ID Nos. 2 and 4) and Neeper et al. teaches the region corresponding to the V domain. The Examiner has expressed concern that "it is unpredictable which part of the molecule would be functional." Claim 1 has been amended to recite the V domain rather than RAGE and thus, applicants believe that they have addressed the Examiner's concern.

Polypeptides derived from the V-domain which are capable of inhibiting the interaction between AGE and RAGE may be identified by first making mutants of the polypeptide, which the Examiner has conceded is routine to one of ordinary skill in the art and secondly, determining if a particular mutant is capable of inhibiting the interaction between AGE and RAGE. This determination may be easily made by using known in vitro binding assays of AGE and RAGE. See the Experimental Procedures, Cell Binding Studies in Schmidt et al. (1992) Isolation and Characterization of Two Binding Proteins for Advanced Glycosylation End Products from Bovine Lung Which Are Present On the Endothelial Cell Surface, J. Biol. Chem. 267(21):14987-14997 attached hereto as **Exhibit D**. Thus, the V-domain itself is an example of a polypeptide which would be useful in carrying out the presently claimed invention. In addition, an amino acid sequence which has peptidomimetic terminal residues would also be an example of such a polypeptide useful in the present invention. Applicants maintain that one of ordinary skill in the art would have been able to carry out the claimed invention in view of applicants' specification and the state of the art at the time of filing. Since applicants have amended claims 1 and 19 to include reference to the V-domain rather than the full length of sRAGE, applicants maintain that it would <u>not</u> constitute undue experimentation for one of ordinary skill in the art to carry out the claimed invention.

As to the Examiner's concern regarding enablement of "to prevent accelerated atherosclerosis in a subject predisposed thereto" and "to prevent macrovessel disease in a subject predisposed thereto," applicants respectfully traverse. Applicants have amended claims 1 and 19 to more particularly point out the presently claimed invention and to address the Examiner's concerns. The specification fully enables the aforementioned claims 1 and 19 and claims dependent therefrom. The Examiner alleges that there is "no clear parameter defining who is

predisposed to develop" atherosclerosis (see page 5, lines 6-7 of the office action). On the contrary, applicants urge that one of ordinary skill in the art would have a reasonable expectation of success in carrying out the claimed invention in view of the known risk factors and physical, biochemical, hereditary, medical and cellular characteristics known to correspond to a subject being predisposed to atherosclerosis or macrovessel disease. The claimed invention is directed to "prevention of accelerated development atherosclerosis" which is a prevention of the worsening of the condition or progression of the disease at an accelerated rate which is common in diabetics, for example, not complete prevention of the genesis of atherosclerosis or atherogenic lesions in a completely healthy individual.

AGEs are present in the early, middle and late stages of atherosclerosis in the absence of diabetes. See Ritthaler et al. (March 1995) Expression Of Receptors For Advanced Glycation End Products In Peripheral Occlusive Vascular Disease, *Am J. Path* 146(3):688-694 (attached hereto as **Exhibit E**). See page 689, column 1, first full paragraph. As to the Examiner's concern regarding non-diabetic subjects, applicants maintain that such an interaction between AGE and RAGE is believed in the art to contribute to the atherosclerotic lesions. See for example, Palinski et al. (1995) Immunological Evidence for the Presence of Advanced Glycosylation End Products In Atherosclerotic Lesions of Euglycemic Rabbits, Arteriosclerosis, *Thrombosis and Vascular Biology* 15(5):571-582 a copy of which is attached hereto as **Exhibit F**.

In sum, in view of the amendments and the discussion, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner noted claims 1-35 remain rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner noted claims 1 and 19 and their dependent claims 2-18 and 20-35, remain indefinite for the reasons of record, because they recite a "polypeptide derived from soluble receptor for advanced glycation product," without providing the metes and bounds of what is encompassed by "derived." Such term might for example encompass mutated forms, chemical modifications, conjugates, cross linked forms, etc...

The Examiner further noted applicants' arguments have been considered but are not found persuasive, because they do not provide structural characteristics for a "derived" polypeptide, and do not recite what is the part of the soluble receptor that binds to AGEs and what part of the soluble receptor the derived polypeptide comes from. The Examiner stated that the specification provides a list that encompasses an unlimited number of structures to choose from (including analogs and peptidomimetic compounds which may be at least partially unnatural (page 10-11), but does not define the metes and bounds and the structural characteristics of the derived polypeptide allowing to define the invention.

In reply, applicants respectfully traverse the rejection and refer to the amendments made hereinabove.

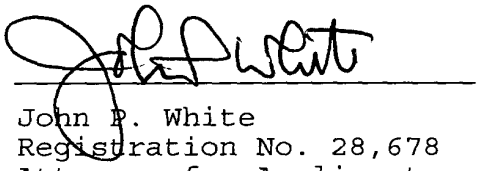
Applicants have amended claims 1 and 19 to include a feature of the polypeptide as follows: comprising the V-domain of sRAGE or a derivative thereof capable of inhibiting the interaction between AGE and RAGE. One of ordinary skill in the art at the

time of filing would know how to carry out binding assays to determine whether or not a derivative of the V-domain of sRAGE would or would not be capable of inhibiting the interaction between AGE and RAGE. Such binding assays are well described as discussed hereinabove (see Exhibit D). The metes and bounds of "derivative" are plainly described in the specification. On page 12, line 21 to page 13, line 1 the specification gives numerous examples of peptidomimetic compounds. The Examiner is further directed to page 10, line 11 to page 11, line 12 wherein a detailed description of many possible embodiments which are encompassed by the present invention are described. The form of a polypeptide which is a derivative of the V-domain of the sRAGE may include the many types of derivatizations disclosed in the subject specification and those known to one of ordinary skill at the time of filing. However, applicants have applied functional metes and bounds in that such a derivative must be capable of inhibiting the interaction between AGE and RAGE. In view of the above amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

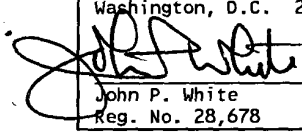
No fee other than the $55.00 extension of time fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents
Washington, D.C. 20231



10/25/99

John P. White Date
Reg. No. 28,678